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09/674,975	11/07/2000	David B. Agus	MSKP039	8051

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EXAMINER	
UNGAR, SUSAN NMN	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/674,975	Applicant(s) Agus et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 23, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *9-13, 16, 17, and 21-24* is/are pending in the application.

4a) Of the above, claim(s) *11-in-part drawn to SEQ ID NO:2* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *9, 10, 11-in-part drawn to SEQ ID NO:1, 12-13, 16-17, 21-24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed April 23, 2003 (Paper No. 11) in response to the Office Action of March 25, 2003 (Paper No. 10) is acknowledged and has been entered. Claims 9-10, 11-in-part as drawn to SEQ ID NO:1, 12, 13, 16-17, 21-24 are currently under prosecution

2. The response (Paper No. 11) to the restriction requirement of March 25, 2003 (Paper No. 10) has been received. Applicant has elected Group I, claims 9-11 the species drawn to a method of active vaccination against B cells expressing CD20 wherein the vaccine composition comprises a peptide derived from human CD20, SEQ ID NO:1 for examination with traverse.

It is here noted that the restriction requirement was not to a species election, but rather is drawn to the election of an inventive group. Please see MPEP 804.01 for further information on linked inventions.

The traversal is on the ground(s) that (a) the restriction requirement is not in accordance with PCT practice and that no explanation of why there is a lack of unity has been cited in the restriction requirement, (b) the recitation of Inventions III-VII as materially distinct methods is confusing since these inventions were not included in the restriction requirement, (c) apparently based on these arguments Applicant requests consideration of all of the claims or a complete explanation as to why there is allegedly a lack of unity of invention to facilitate review of the restriction requirement.

(a) and (c) Upon review it is found that Applicant is correct, the restriction requirement mailed March 25, 2003 (Paper No. 10) was not prepared in accordance with PCT practice. Under PCT practice, Groups I and II are not groups under US

linking claim practice for the reasons set forth below, but rather are drawn to Group I, claims 9-10 and 11-in-part, SEQ ID NO:1 and Group II, claims 9-10 and 11-in-part, SEQ ID NO:2 and are separate groups for the reasons set forth below. Further, a complete explanation as to why there is a lack of unity of invention is set forth below and all of the claims will not be examined for the reasons set forth below, (b) although Applicant has stated that the reference to Inventions III-VII is confusing, given the recitation of the methods of the instant invention in the section directly above Section 3, page 4, the recitation of inventions III-VII, rather than inventions I and II is an inadvertent typographical error and it is clear that the burden demonstrated in Section 3, page 4 under US Practice was intended to refer to Inventions I and II.

The reasons why the inventions lack unity are set forth as follows:

3. Groups I and II are not so linked as to form a single inventive concept under PCT Rule 13 because:

(A) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for

carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476 (c).

Therefore, the inventions listed as Groups I and II do not have unity of invention and they do not relate to a single inventive concept because they are not drawn to any of the categories listed. That is Group I is drawn to a product, SEQ ID NO:1 and a method of using said product. Group II is drawn to a different product and a method of using that product.

(B) Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features which define a contribution over the prior art. If there is no special technical feature, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

The technical feature linking Groups I-II appears to be that they both relate to a method of active vaccination with CD20 polypeptides against B-cell non-Hodgkin's lymphoma. In particular, Group I is drawn to a method for active vaccination against B cells expressing CD20/treatment of B cell non-Hodgkin's lymphoma and a vaccine composition comprising at least an immunogenic portion of the extracellular domain of the CD20, SEQ ID NO:1 coupled to or administered

with KLH and a pharmaceutically acceptable adjuvant. However, Maloney et al (Blood, 1994, 84:2457-2466) specifically teach that the B-cell antigen CD20 is an excellent target for antibody-directed therapies for recurrent B-cell lymphoma, non-Hodgkin's lymphoma and teach successful passive immunization treatment of non-Hodgkin's lymphoma (see abstract). Further, Maloney et al specifically teach that with current technology, because of the difficulty and time required to produce patient-specific antibodies, this approach is not feasible for general application. Although Maloney et al do not teach active vaccination against B cells expressing CD20/treatment of B cell non-Hodgkin's lymphoma and a vaccine comprising an immunogenic portion of the extracellular domain of CD20, SEQ ID NO:2 coupled to or administered with KLH and a pharmaceutically acceptable adjuvant, Kwak et al (New England J. Med., 306:517-522, 1992) specifically teach the effective treatment of B-cell lymphoma, non-Hodgkin's lymphoma, by administration of active vaccine to a patient wherein the vaccine comprises autologous immunoglobulin-idiotype protein antigen isolated from B-cell lymphoma conjugated to KLH, a strongly immunogenic carrier protein, and an adjuvant (see abstract, p. 1209 col 2 and p. 1210, col 1) and teaches that active immunization leads to the induction of a polyclonal antibody immune response against the antigen to treat the B-cell lymphoma (p. 1214, col 1). The reference further teaches that a potential limitation of this approach is that the use of autologous immunoglobulin-idiotype protein requires that a vaccine be produced individually from each patient and that accessible tumor tissue be available as starting material (p. 1215, col 1). US Patent No. 5,830,731 specifically teaches that the proteins of the invention, including a

polypeptide comprising SEQ ID NO:1 (see sequence search report us-09-674-975-1.rag and Figure 10A/B) are useful for immunotherapeutic applications including the treatment of plasma neoplasms and treatment of immune-mediated diseases (which clearly read on B-cell lymphoma) wherein the substantially pure proteins of the invention, including the CD20 antigen may be administered alone or in combination with other antigens (col 7, lines 29-40 and col 20, lines 29-55). Further, the antigens of the invention, including the CD20 antigen, may be prepared as a pharmaceutical composition for human therapy which is administered together with one or more acceptable carriers (col 21, lines 25-39). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the CD20 antigen of US Patent No. 5,830,731 for the antigen of Kwak et al in the method of Kwak et al and to produce a vaccine composition comprising the CD20 antigen of US Patent No. 5,830,731 conjugated to KLH and an adjuvant and then to use that composition for the treatment of patients with non-Hodgkin's lymphoma with a reasonable expectation of success because Maloney et al specifically teach that CD20 is an excellent target for antibody-directed therapies for recurrent B-cell lymphoma, Kwak et al specifically teach that active immunization induces a polyclonal immune response to antigen and US Patent No. 5,830,731 specifically teaches that the administration of CD20 antigen in combination with a suitable carrier is useful for treatment of plasma related neoplasms. One would have been motivated to substitute the CD20 antigen of US Patent No. 5,830,731 for the antigen of Kwak et al because both Maloney et al and Kwak et al teach the problems associated with the use of autologous, patient

specific antigens for the treatment of B-cell lymphoma and further because active immunization with the CD20 antigen of US Patent No. 5,830,731 would lead to a polyclonal antibody immune response that would target CD20 on B cell lymphoma cells which were known to be excellent targets for the antibody treatment of non-Hodgkin's lymphoma.

Therefore, the technical feature linking the inventions of Groups I-II does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

In view of the above, Group I is considered the main invention. After that, all other products and methods have been broken out as separate groups (see 37 CAR 1.475(d)) and the previous restriction requirement is maintained.

However, upon review and reconsideration and in view of the art found during the search of the first invention, it is found that examination of Claims 12-13, 16-17, 21-24 do not impose a serious burden on the examiner and they are hereby rejoined to Group I, which now consists of Claims 9-10, 11-in-part, SEQ ID NO:1, 12-13, 16-17, 21-24.

It is again noted that the response demonstrates that Applicant fully understands the issues in this case and that Applicant has made a full response to the restriction requirement by electing the invention to be searched. Examiner has remedied the deficiencies in the previous restriction requirement and has provided a complete explanation of the reasons why unity of invention is lacking based on PCT practice. Although Examiner requested Applicant to orally elect an invention on July 18, 2003 (see Interview Summary, Paper No. 12), and informed Applicant that

claims 12-13, 16, 21-24 would be rejoined with claims 9-10 and 11-in-part, SEQ ID NO:1, Applicant declined to make an oral election and requested that a written restriction be mailed. Upon reconsideration and in consultation with a technology center restriction specialist, since Examiner has provided a complete explanation, since Examiner has rejoined claims 12-13, 16, 21-24 to Group I, since Applicant has previously elected the invention of Claims 9-10 and 11-in-part, SEQ ID NO:1, no additional restriction requirement will be mailed and the instant restriction requirement is maintained. Examination of the elected invention together with the rejoined claims is as follows:

Specification

4. The specification on page 1 should be amended to reflect the parent provisional application and its status.

5. The specification is objected to because of an apparent typographical error on page 4, line 27 wherein "protein to direct and immunological response" is disclosed. It appears that the term "an" and not "and" was meant. Clarification and appropriate correction is required.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because there are alterations that have been made in the declaration that are either undated and/or not initialed. In particular, the information for Inventor Agus has been altered and initialed but not

dated. Further, the information for Inventor Roberts has been altered but neither initialed nor dated. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

8. Claims 9-10, 11-in-part as drawn to SEQ ID NO:1, 12-13, 16-17, 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for active vaccination against B cells expressing CD20/a method for treatment of B cell non-Hodgkin's lymphoma (NHL) comprising administering a vaccine composition comprising an immunogen consisting of SEQ ID NO:1 or full length CD20 coupled to KLH and an adjuvant and the composition comprising said immunogen does not reasonably provide enablement for a method for active vaccination against B cells expressing CD20/a method for treatment of NHL comprising administering a vaccine composition comprising at least an immunogenic portion of the extracellular domain of CD20, a peptide comprising SEQ ID NO:1, KLH and an adjuvant and the composition comprising said vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, use the invention commensurate in scope with these claims.

The claims are drawn to a method for active vaccination against B cells expressing CD20/a method for treatment of NHL comprising administering a vaccine composition comprising at least an immunogenic portion of the extracellular domain of CD20, a peptide comprising SEQ ID NO:1, KLH and an adjuvant and the composition comprising said vaccine. The specification teaches that NHL is treated by the administration of CD20 itself or an immunogenic fragment of the extracellular portion thereof coupled to or administered with an antigenic carrier such as KLH (p. 2, lines 20-25). This results in the stimulation of the production of polyclonal antibodies against CD20 or an immunogenic fragment thereof which has the affect of reducing the number of B-cells, including malignant B-cells (p. 2, lines 25-27). A peptide antigen is prepared which contains at least an immunogenic portion of the extracellular domain of CD20. A suitable fragment is the 44 amino acid peptide spanning amino acids 136-179 of the sequence of human CD20. Other immunogenic fragments derived from the extracellular domain of CD20 may also be used (p. 4, lines 9-19). An immunogenic fragment is a molecule which includes at least a portion of the extracellular domain to direct an immunological response to that transmembrane protein when the immunogenic fragment is coupled to or administered with an antigenic carrier protein effective to break tolerance and administered with an adjuvant (p. 4, lines 24-30). When a peptide of the extracellular human CD20, SEQ ID NO:1, is coupled to KLH and administered with an adjuvant to mice, antibodies which react with CD20 are found in plasma and these antibodies react to cells which express CD20. Further, B cells in the mice are depleted (p. 5, lines 16-24). This is exemplified in Examples 1, 2 and 6, pages

8-11 wherein an immunogen consisting of SEQ ID NO:1 is coupled to KLH and administered with adjuvant. The specification further teaches that it is possible that T cell mediated effector mechanisms are involved in the immune response. As evidence of this, human peptide sequences capable of binding to the corresponding human histocompatability antigens are illustrated in Table 1. This information was derived from a search of the NIH Bioinformatics and Molecular Analysis Section HLA Binding Predictions database. Applicant points to Table 1 wherein putative peptide sequences that will bind to HLA molecules, including Kd, are disclosed.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is well known in the art that it is unpredictable that production of antibodies from linear fragments of amino acid sequences will in fact produce antibodies that will bind to the wild-type amino acid sequence as it is exposed on the cell surface. In particular, Roitt et al, 1998, Immunology, 4th ed, Mosby, London teach the unpredictability of immunogenicity of any particular fragment and teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to

the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which part of the protein, other than SEQ ID NO:1 should be used to produce antibodies which will bind specifically to CD20 on a tumor cell surface.

Moreover, the claims as written are drawn to immunogens which define specific epitopes of CD20. However, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, other than SEQ ID NO:1, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes that would function as claimed in active vaccination. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as

evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Since the specification has not identified which amino acids and or polypeptide fragments other than SEQ ID NO:1 have the critical or essential characteristics of the encompassed epitopes, one would not know how to make the claimed invention and it would not be predictable, that the broadly claimed methods and compositions would function as claimed.

Further as drawn specifically to a T-cell component of the vaccination method and composition, Hooijberg et al (J. Immunotherapy with Emphasis on Tumor Immunology, 1996, 19(5)346-356) specifically teach that peptide sequences predicted to bind HLA motifs in mouse CD20 (p. 348, col 1, see Selection of Peptides) were synthesized subsequently tested for binding to HLA molecules, wherein it was found that only two of ten peptides successfully bound to the HLA molecules and were capable of producing peptide specific *in vivo* T lymphocyte responses (see Table 1, page 349). When assayed, it was found that CTL produced by these peptides were unable to kill syngeneic B cell tumor line cells, although a single CD19 peptide induced CTL was able to kill the cells of the same syngeneic B cell tumor line (p. 350, col 1 and abstract). The authors speculate that there was either a failure of processing and/or presentation of these two peptides by this cell line. It appears that the ability to produce CTL specific for a particular antigen, even with conventionally generated predictions is unpredictable and that each

peptide must be individually assayed in order to determine whether or not it will function to produce CTL which bind not only to the peptide but also to the antigen of interest. It appears that the artisan is left to random experimentation in order to determine which peptide would function as claimed. Random experimentation is undue. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention

Finally, as drawn to administration of the peptide with KLH, but in the absence of coupling of the KLH to the peptide, Helling et al., (Can. Res., 1994, 197-203), although drawn to active vaccination with gangliosides, the teachings of Helling et al are clearly relevant to the instant application. Helling et al specifically teach that vaccination with KLH conjugated to the active immunogen specifically resulted in effective antibody production of both the IgG and IgM type, while vaccination with the active immunogen alone did not induce the production of antibodies of either type. The reference reveals that vaccination with immunogen and KHL mixed together resulted in only a weak IgM response and no IgG response and that immunogen conjugated to KLH showed the strongest response(see Table 1, page 199 and the paragraph bridging pages 199-200). In addition, the reference teaches that conjugation of poorly immunogenic antigens to highly immunogenic carrier molecules is a well-known approach to augmenting immunogenicity (p. 201, col 1). The reference concludes that the production of IgG antibodies is associated with a T-cell dependent pathway and teaches that the induction of IgG1 subclass indicates that mechanism of the vaccine includes the recruitment of some T-cells. Although drawn to a different immunogen, there is clearly a difference between the

antibody response to immunogen administered together with KLH and immunogen conjugated to KLH. It would be expected that the same difference would be seen with any immunogen. Given that no IgG induction was found without conjugation of KLH to the immunogen, given that the IgM response was weak, given that the specification provides no guidance as to the effective induction of an immune response to CD20 without conjugation of KLH to SEQ ID NO:1, it cannot be predicted whether or not unconjugated SEQ ID NO:1 or any other CD20 extracellular fragment would induce a sufficient response to function as claimed. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 9-10, 11-in-part drawn to SEQ ID NO:1, 12-13, 16-17, 21-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Maloney et al (Blood, 1994, 84:2457-2466), *Supra* in view of Kwak et al (New England J. Med., 306:517-522, 1992), *Supra* and US Patent No. 5,830,731 , *Supra.*

It is noted that the recitation of the limitation "having the sequence" is read for examination purposes as broad language and thus the claims are read as "comprising the sequence".

The claims are drawn to a method for active vaccination against B cells expressing CD20/a method for the treatment of B cell non-Hodgkin's lymphoma comprising administering to a patient a vaccine composition comprising at least an immunogenic portion of the extracellular domain of CD20, SEQ ID NO:1, coupled to or administered with a carrier protein effective to break tolerance to the transmembrane protein and a pharmaceutically acceptable adjuvant, wherein the carrier is KLH, wherein the peptide composition comprises a peptide having the sequence given by SEQ ID NO:1.

Maloney et al specifically teach that the B-cell antigen CD20 is an excellent target for antibody-directed therapies for recurrent B-cell lymphoma, non-Hodgkin's lymphoma and teach successful passive immunization treatment of non-Hodgkin's lymphoma (see abstract). Further, Maloney et al specifically teach that with current technology, because of the difficulty and time required to produce patient-specific antibodies, this approach is not feasible for general application. Maloney et al teach as set forth above but do not teach active vaccination against B cells expressing CD20/treatment of B cell non-Hodgkin's lymphoma and a vaccine comprising an immunogenic portion of the extracellular domain of CD20, SEQ ID NO:1 coupled to or administered with KLH and a pharmaceutically acceptable adjuvant,

Kwak et al specifically teach the effective treatment of B-cell lymphoma, non-Hodgkin's lymphoma, by administration of active vaccine to a patient wherein the vaccine comprises autologous immunoglobulin-idiotype protein antigen isolated from B-cell lymphoma conjugated to KLH, a strongly immunogenic carrier protein, and an adjuvant (see abstract, p. 1209 col 2 and p. 1210, col 1) and teaches that active immunization leads to the induction of a polyclonal antibody immune response against the antigen to treat the B-cell lymphoma (p. 1214, col 1). The reference further teaches that a potential limitation of this approach is that the use of autologous immunoglobulin-idiotype protein requires that a vaccine be produced individually from each patient and that accessible tumor tissue be available as starting material (p. 1215, col 1).

US Patent No. 5,830,731 specifically teaches that the proteins of the invention, including a polypeptide comprising SEQ ID NO:1 (see sequence search

report us-09-674-975-1.rag and Figure 10A/B) are useful for immunotherapeutic applications including the treatment of plasma neoplasms and treatment of immune-mediated diseases (which clearly read on B-cell lymphoma) wherein the substantially pure proteins of the invention, including the CD20 antigen may be administered alone or in combination with other antigens (col 7, lines 29-40 and col 20, lines 29-55). Further, the antigens of the invention, including the CD20 antigen, may be prepared as a pharmaceutical composition for human therapy which is administered together with one or more acceptable carriers (col 21, lines 25-39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the CD20 antigen of US Patent No. 5,830,731 for the antigen of Kwak et al in the method of Kwak et al and to produce a vaccine composition comprising the CD20 antigen of US Patent No. 5,830,731 conjugated to KLH and an adjuvant and then to use that composition for the treatment of patients with non-Hodgkin's lymphoma with a reasonable expectation of success because Maloney et al specifically teach that CD20 is an excellent target for antibody-directed therapies for recurrent B-cell lymphoma, Kwak et al specifically teach that active immunization induces a polyclonal immune response to antigen and US Patent No. 5,830,731 specifically teaches that the administration of CD20 antigen in combination with a suitable carrier is useful for treatment of plasma related neoplasms. One would have been motivated to substitute the CD20 antigen of US Patent No. 5,830,731 for the antigen of Kwak et al because both Maloney et al and Kwak et al teach the problems associated with the use of autologous, patient specific antigens for the treatment of B-cell lymphoma and

further because active immunization with the CD20antigen of US Patent No. 5,830,731 would lead to a polyclonal antibody immune response that would target CD20 on B cell lymphoma cells which were known to be excellent targets for the antibody treatment of non-Hodgkin's lymphoma.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
July 24, 2003